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Intellectual Property Dept.
Dewitt Ross & Stevens SC
2 East Mifflin Street
Suite 600
Madison, WI 53703-2865

EXAMINER	
DUNSTON, JENNIFER ANN	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,416	ANSARI, ASEEM Z.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,13,15-19,22,24-28,31,32,34-36 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,13,15-19,22,24-28,31,32,34-36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Any rejection of record in the previous office actions not addressed herein is withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 11/29/2007. Therefore, this action is not final.

This action is in response to the amendment, filed 5/22/2008, in which claims 5, 14 and 23 were canceled, and claims 1, 6, 7, 13, 15, 16, 22, 24, 25, 31, 34, 35, 36 and 38 were amended. Currently, claims 1-4, 6-10, 13, 15-19, 22, 24-28, 31, 32, 34-36 and 38 are pending and under consideration.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

Page 24 (lines 28 and 30), page 35 (line 12), page 36 (line 14), page 37 (line 18), and page 39 (line 3) contain peptide sequences that are not referred to by the use of a sequence identifier. Where the description or claims of a patent application discuss a sequence that is set forth in the Sequence Listing, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In response to this office action, Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. The nature of the non-compliance did not preclude an examination of the elected invention on the merits, the results of which are presented below.

Specification

The disclosure is objected to because of the following informalities:

Page 37 contains a drawing, which contains a graphical view of an Exd protein bound to a nucleic acid and test compound of the invention. The specification shall not contain drawings. See 37 CFR 1.58(a). While the specification may contain chemical formulas, graphical illustrations must be submitted as drawings in accordance with 37 CFR 1.81.

Appropriate correction is required.

Claim Objections

Claims 16, 17, 25 and 26 are objected to because of the following informalities: the claims contain a duplication of the word step (i.e., the phrase "step step"). It would be remedial to delete the extra word to improve the grammar of the claim. Appropriate correction is required.

Claim 34 is objected to because of the following informalities: the word "excluding" at line 3 is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 19, 22, 24-28, 32 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claims 10, 19, 28, 32 and 36 limit the linker moiety to an "aptamer." The specification recognizes that the term "aptamer" generally refers to a double-stranded DNA or single-stranded RNA moiety that binds to a specific molecular target (see page 12, lines 13-15). However, the present specification defines the term "aptamer" to have a broader meaning encompassing (but not limited to) a linker moiety that is dimensioned and configured to bind specifically with a small-molecule binding partner (see page 12, lines 15-18). The specification does not provide an explicit definition for the term, but indicates that it is broader than the definition usually given to the term. The specification does not describe the differences between a linker moiety, in general, and a linker moiety that is an aptamer. Because dependent claims are presented that are specifically intended to limit the linker moiety to an aptamer (e.g., claims 10, 19, 28 and 32), it is clear that there should be some structural differences between a "linker moiety" and an "aptamer." However, these differences are unclear. Accordingly, the metes and bounds of the claims are unclear.

Claim 22 is vague and indefinite in that the metes and bounds of the claimed method are unclear. The preamble recites a "method of evaluating one or more test compounds to identify test compounds that facilitate, recruit, or stabilize binding of sequence-specific transcription factors to corresponding single-, double-, or triple-stranded transcription factor binding sites on nucleic acid." However, it is not clear that the methods will *necessarily* result in the

identification of compounds that facilitate, recruit, or stabilize binding of sequence-specific transcription factors to corresponding single-, double-, or triple-stranded transcription factor binding sites on nucleic acid. Claim 22, step (a) part (iii) requires the test compound in the assay to be "known to modulate binding of natural transcription factors to the transcription factor binding site defined in the nucleic acid target." Thus, the compounds screened in the assay must be known to have the function identified by the assay. It is not clear what is accomplished by performing the claimed method steps, and the metes and bounds of the claim are unclear.

Claims 24-28 depend from claim 22 and thus are indefinite for the same reasons applied to claim 22.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 6-10, 31, 32, 34-36 and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanojevic (US Patent Application Publication NO. 2003/105045). This is a new rejection.

Regarding claim 1, Stanojevic teaches a method for assaying a test compound for activity as a transcriptional effector. Stanojevic teaches that the method includes (i) providing a DNA template, which comprises one and only one binding site for a sequence specific regulatory

factor that binds to the TATA box, where the nucleic acid target has conjugated thereto outside the TATA box, an anchor moiety, which is a non-peptidic DNA binding domain, a flexible linker domain covalently bound to the anchor moiety and a test compound; (ii) contacting the test composition with a transcription mixture including a DNA template, a eukaryotic RNA polymerase molecule capable of forming a complex with the test composition and the DNA template, a buffer and substrates under conditions suitable for RNA synthesis, such that RNA is synthesized; and (iii) determining the quantity of RNA produced in the presence of the test composition compared to a level in the absence of the test composition, which is a measure of the activity of the test composition as a transcriptional modulator (e.g., paragraph [0021]; Figure 6A).

The claims require that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target. However, the specification does not provide a specific description of characteristics that an entropically destabilized linker would possess, except for length (see page 39, line 16 to page 40, line 6). Since Stanojevic teaches linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional behavior on the nucleic acid target. As written the claim does not include a step that measures conditional behavior at different temperatures.

Regarding claim 2, Stanojevic teaches that the anchor moiety (non-peptidic DNA binding domain) can comprise a polyamide (e.g., paragraph [0046]).

Regarding claims 3 and 6, Stanojevic teaches that the anchor moiety (non-peptidic DNA binding domain) can comprise a major-groove-binding, triple-helix-forming oligonucleotide, or a

peptide analog such as a polyamide, for example (e.g., paragraphs [0046], [0013]-[0014], [0042]-[0046]).

Regarding claims 7and 8, Stanojevic teaches that the linker is a bifunctional moiety comprised mainly of carbons, hydrogen, nitrogen, oxygen, sulfur and phosphorous, where suitable linkers include flexible moieties, such as polyglycols, including polyethylene glycol, or other polyalkoxy moieties, or oligomers derived from monomers of nucleotides, natural or non-natural amino acids and lower alkyls, and preferably oxygen-containing organic moieties (e.g., paragraphs [0061]-[0065]; Figure 2A).

Regarding claim 9, Stanojevic teaches that the anchor moiety (non-peptidic DNA binding domain) can comprise a major-groove-binding, triple-helix-forming oligonucleotide, or a peptide analog such as a polyamide, for example (e.g., paragraphs [0046], [0013]-[0014], [0042]-[0046]).

Regarding claim 10, the claim limits the linker moiety to an "aptamer." The specification recognizes that the term "aptamer" generally refers to a double-stranded DNA or single-stranded RNA moiety that binds to a specific molecular target (see page 12, lines 13-15). However, the present specification defines the term "aptamer" to have a broader meaning encompassing a linker moiety that is dimensioned and configured to bind specifically with a small-molecule binding partner (see page 12, lines 15-18). The specification does not provide an explicit definition for the term, but indicates that it is broader than the definition usually given to the term. Accordingly, the term "aptamer" is reasonably interpreted to encompass other linker structures that do not necessarily bind a small-molecule. Stanojevic teaches the artificial transcription factor where the linker is comprised mainly of carbons, hydrogen, nitrogen, oxygen,

sulfur and phosphorous, where suitable linkers include flexible moieties, such as polyglycols, or other polyalkoxy moieties, or oligomers derived from monomers of nucleotides, natural or non-natural amino acids and lower alkyls, and preferably oxygen-containing organic moieties (e.g., paragraph [0061]).

Regarding claims 31 and 34, Stanojevic teaches an artificial transcription factor that comprises a non-peptidic DNA binding domain, a flexible linker, and a transcriptional effector, one end of the linker being covalently bound to the DNA binding domain, and the other end of the linker being covalently bound to the transcriptional effector (e.g., paragraph [0011]). Further, Stanojevic teaches the further inclusion of one moiety that is a spacer or anchor molecule that allows the covalent attachment of the linker to the non-peptidic DNA binding domain (e.g., paragraphs [0063] and [0066]). Stanojevic teaches the artificial transcription factor where the linker is 10-100 Å, in the range of 25-40 Å, in the range of 40-60 Å, or in the range of 60-100 Å (e.g., paragraph [0011]). The rejected claim requires an isolated nucleic acid target that defines one and only one desired or putative binding site for a sequence-specific regulatory factor, excluding binding sites for transcriptional machinery, the isolated nucleic acid target having covalently bonded thereto, at a point proximate to the binding site, one an only one anchor moiety, a linker moiety covalently bound to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive, conditional behavior upon the isolated nucleic acid target, and a test compound conjugated to the linker moiety. Each of the claimed elements is present in the artificial transcription factor taught by Stanojevic. With respect to the binding site, Stanojevic teaches non-peptidic DNA binding domains that are single stranded nucleic acid sequences (e.g.,

Table 1; paragraphs [0042], [0045] and [0066]). The claims do not limit the target nucleic acid sequence to a particular sequence for a specific sequence-specific transcription factor. The claims require the sequence to "define one and only one desired or putative binding site for a sequence-specific regulatory factor." The single-stranded DNA taught by Stanojevic falls within the scope of a desired or putative binding site for a sequence-specific transcription factor. Stanojevic teaches the use of one anchor moiety to covalently attach the single-stranded DNA to the flexible linker moiety.

The claims require that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target. However, the specification does not provide a specific description of characteristics that an entropically destabilized linker would possess, except for length (see page 39, line 16 to page 40, line 6). Since Stanojevic teaches linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional behavior on the nucleic acid target.

Regarding claim 32, the claim limits the linker moiety to an "aptamer." The specification recognizes that the term "aptamer" generally refers to a double-stranded DNA or single-stranded RNA moiety that binds to a specific molecular target (see page 12, lines 13-15). However, the present specification defines the term "aptamer" to have a broader meaning encompassing a linker moiety that is dimensioned and configured to bind specifically with a small-molecule binding partner (see page 12, lines 15-18). The specification does not provide an explicit definition for the term, but indicates that it is broader than the definition usually given to the term. Accordingly, the term "aptamer" is reasonably interpreted to encompass other linker

structures that do not necessarily bind a small-molecule. Stanojevic teaches the artificial transcription factor where the linker is comprised mainly of carbons, hydrogen, nitrogen, oxygen, sulfur and phosphorous, where suitable linkers include flexible moieties, such as polyglycols, or other polyalkoxy moieties, or oligomers derived from monomers of nucleotides, natural or non-natural amino acids and lower alkyls, and preferably oxygen-containing organic moieties (e.g., paragraph [0061]).

Regarding claim 35, Stanojevic teaches a kit comprising instructions and one or more containers holding a precursor composition having a flexible linker covalently bound to a DNA binding domain, where the precursor composition contains a reactive end group that can be used to couple the precursor compound to a test compound of interest (e.g., paragraph [0076]). Stanojevic teaches an artificial transcription factor that comprises a non-peptidic DNA binding domain, a flexible linker, and a transcriptional effector, one end of the linker being covalently bound to the DNA binding domain, and the other end of the linker being covalently bound to the transcriptional effector (e.g., paragraph [0011]). Further, Stanojevic teaches the further inclusion of one moiety that is a spacer or anchor molecule that allows the covalent attachment of the linker to the non-peptidic DNA binding domain (e.g., paragraphs [0063] and [0066]). Stanojevic teaches the artificial transcription factor where the linker is 10-100 Å, in the range of 25-40 Å, in the range of 40-60 Å, or in the range of 60-100 Å (e.g., paragraph [0011]). The rejected claim requires an isolated nucleic acid target that defines one and only one desired or putative binding site for a sequence-specific regulatory factor, excluding binding sites for transcriptional machinery, the isolated nucleic acid target having covalently bonded thereto, at a point proximate to the binding site, one an only one anchor moiety, a linker moiety covalently

bound to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive, conditional behavior upon the isolated nucleic acid target, and a test compound conjugated to the linker moiety. Each of the claimed elements is present in the artificial transcription factor taught by Stanojevic. With respect to the binding site, Stanojevic teaches non-peptidic DNA binding domains that are single stranded nucleic acid sequences (e.g., Table 1; paragraphs [0042], [0045] and [0066]). The single-stranded DNA taught by Stanojevic falls within the scope of the claimed nucleic acid target. Stanojevic teaches the use of one anchor moiety to covalently attach the single-stranded DNA to the flexible linker moiety.

Regarding claims 36 and 38, Stanojevic teaches a kit comprising instructions and one or more containers holding a precursor composition having a flexible linker covalently bound to a DNA binding domain, where the precursor composition contains a reactive end group that can be used to couple the precursor compound to a test compound of interest (e.g., paragraph [0076]). Stanojevic teaches an artificial transcription factor that comprises a non-peptidic DNA binding domain, a flexible linker, and a transcriptional effector, one end of the linker being covalently bound to the DNA binding domain, and the other end of the linker being covalently bound to the transcriptional effector (e.g., paragraph [0011]). Further, Stanojevic teaches the further inclusion of one moiety that is a spacer or anchor molecule that allows the covalent attachment of the linker to the non-peptidic DNA binding domain (e.g., paragraphs [0063] and [0066]). Stanojevic teaches the artificial transcription factor where the linker is 10-100 Å, in the range of 25-40 Å, in the range of 40-60 Å, or in the range of 60-100 Å (e.g., paragraph [0011]). The rejected claim requires an isolated nucleic acid target that defines one and only one desired or

putative binding site for a sequence-specific regulatory factor, excluding binding sites for transcriptional machinery, the isolated nucleic acid target having covalently bonded thereto, at a point proximate to the binding site, one an only one anchor moiety, a linker moiety covalently bound to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive, conditional behavior upon the isolated nucleic acid target, and a test compound conjugated to the linker moiety. Each of the claimed elements is present in the artificial transcription factor taught by Stanojevic. With respect to the binding site, Stanojevic teaches non-peptidic DNA binding domains that are single stranded nucleic acid sequences (e.g., Table 1; paragraphs [0042], [0045] and [0066]). The single-stranded DNA taught by Stanojevic falls within the scope of the claimed nucleic acid target. Stanojevic teaches the use of one anchor moiety to covalently attach the single-stranded DNA to the flexible linker moiety.

The claim limits the linker moiety to an "aptamer." The specification recognizes that the term "aptamer" generally refers to a double-stranded DNA or single-stranded RNA moiety that binds to a specific molecular target (see page 12, lines 13-15). However, the present specification defines the term "aptamer" to have a broader meaning encompassing a linker moiety that is dimensioned and configured to bind specifically with a small-molecule binding partner (see page 12, lines 15-18). The specification does not provide an explicit definition for the term, but indicates that it is broader than the definition usually given to the term. Accordingly, the term "aptamer" is reasonably interpreted to encompass other linker structures that do not necessarily bind a small-molecule. Stanojevic teaches the artificial transcription factor where the linker is comprised mainly of carbons, hydrogen, nitrogen, oxygen, sulfur and

phosphorous, where suitable linkers include flexible moieties, such as polyglycols, or other polyalkoxy moieties, or oligomers derived from monomers of nucleotides, natural or non-natural amino acids and lower alkyls, and preferably oxygen-containing organic moieties (e.g., paragraph [0061]).

Response to Arguments - 35 USC § 102

The rejection of claims 13 and 16-19 under 35 U.S.C. 102(e) as being anticipated by Stanojevic has been withdrawn. Stanojevic does not teach the method where the isolated nucleic acid target is covalently bonded to an anchor moiety. Stanojevic teaches anchor moieties that are non-peptidic DNA binding domains, which become conjugated to a nucleic acid target through non-covalent interactions.

With respect to the rejection of claims 1-3 and 6-10 under 35 U.S.C. 102(e) as being anticipated by Stanojevic, Applicant's arguments filed 5/22/2008 have been fully considered but they are not persuasive.

The response asserts that the transcriptional machinery itself, which transmits the signal to RNA polymerase II to begin or end transcription, is not itself sequence-specific. The response refers to Exhibit A, which refers to "transcriptional machinery" as having the ability to "drive" transcription. The response asserts that the present invention is not directed to measuring transcription *per se*, but to evaluate the mechanism of sequence-specific binding of regulatory factors to their cognate DNA binding sites.

These arguments are not found persuasive. The claims do not positively set forth the action steps used to determine binding of a sequence-specific regulatory factor to the binding site

defined in the nucleic acid target. The claims have been amended to exclude "measuring recruitment of non-sequence-specific transcriptional machinery." The response does not provide specific evidence that the reaction mix of Stanojevic does not contain a sequence-specific regulatory factor that binds the TATA box of the nucleic acid target. It was well known in the art at the time the invention was made that the TATA box sequence is recognized in a sequence-specific manner by the TATA-box binding protein (TBP), an essential factor involved in the initiation of transcription by all three eukaryotic DNA polymerases (Wang et al. PNAS, USA, Vol. 92, pages 8606-8610, September 1995; e.g., Abstract; page 8607, paragraph bridging columns; page 8609, left column, 1st full paragraph). The isolated nucleic acid target taught by Stanojevic comprises one and only one known binding site for TBP, a sequence-specific regulatory factor. Measuring transcription in the assay of Stanojevic is a measure of sequence-specific TBP binding and subsequent recruitment of the transcriptional machinery, and not just a measurement of non-sequence specific requirement of transcriptional machinery.

With respect to the rejection of claims 31, 32, 34-36 and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanojevic, Applicant's arguments filed 5/22/2008 have been fully considered but they are not persuasive.

The response asserts that the amendment of the claims to require an isolated nucleic acid target that comprises "one and only one" binding site and "one and only one" anchor moiety overcomes the rejection. This is not found persuasive. Stanojevic teaches an artificial transcription factor that comprises a non-peptidic DNA binding domain, a flexible linker, and a transcriptional effector, one end of the linker being covalently bound to the DNA binding domain, and the other end of the linker being covalently bound to the transcriptional effector

(e.g., paragraph [0011]). Further, Stanojevic teaches the further inclusion of one moiety that is a spacer or anchor molecule that allows the covalent attachment of the linker to the non-peptidic DNA binding domain (e.g., paragraphs [0063] and [0066]). Stanojevic teaches the artificial transcription factor where the linker is 10-100 Å, in the range of 25-40 Å, in the range of 40-60 Å, or in the range of 60-100 Å (e.g., paragraph [0011]). The rejected claims require an isolated nucleic acid target that defines one and only one desired or putative binding site for a sequence-specific regulatory factor, excluding binding sites for transcriptional machinery, the isolated nucleic acid target having covalently bonded thereto, at a point proximate to the binding site, one an only one anchor moiety, a linker moiety covalently bound to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive, conditional behavior upon the isolated nucleic acid target, and a test compound conjugated to the linker moiety. Each of the claimed elements is present in the artificial transcription factor taught by Stanojevic. With respect to the binding site, Stanojevic teaches non-peptidic DNA binding domains that are single stranded nucleic acid sequences (e.g., Table 1; paragraphs [0042], [0045] and [0066]). The claims do not limit the target nucleic acid sequence to a particular sequence for a specific sequence-specific transcription factor. The claims require the sequence to "define one and only one desired or putative binding site for a sequence-specific regulatory factor." Further, the specification teaches that a target nucleic acid sequence may be single-stranded DNA (e.g., page 9, lines 3-6). The single-stranded DNA taught by Stanojevic falls within the scope of a desired or putative binding site for a sequence-specific transcription factor. Stanojevic teaches the use of one anchor moiety to covalently attach the single-stranded DNA to the flexible linker moiety. Further, the effector

domain of Stanojevic falls within the scope of the claimed test compound. The specification teaches the use of literally any test compound desired (e.g., page 9, lines 17-19). The response asserts that the Office relies upon Figure 6A of the Stanojevic publication, which illustrates a TATA box and five upstream binding sites. These elements are not part of the artificial transcription factor of Stanojevic. Thus, Figure 6A is not relied upon for teaching the compositions of claims 31, 32, 34-36 and 38.

Stanojevic also teaches a kit comprising a flexible linker covalently bound to a DNA binding domain and a reactive end group (i.e. a free terminus) that can be used to couple the construct to a test compound of interest to assess the activity of the composition. Stanojevic teaches that the kit would have instructions for using the precursor compound in the disclosed methods (see paragraph 0076, for example). Kits comprising the flexible linker covalently bound to a DNA binding domain and a reactive end group (i.e. a free terminus) would meet the limitation of a kit and composition of matter wherein the bifunctional linker moiety is an aptamer.

The claims drawn to kits recite that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target. However, the specification does not provide a specific description of characteristics that an entropically destabilized linker would possess except for length (see 0161-0162, for example). Since Stanojevic teaches linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional behavior on the nucleic acid target.

Accordingly, the teachings of Stanojevic meet each of the limitations for claims 1-3, 6-10, 31, 32, 34-36 and 38.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31, 32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al (US Patent No. 5,879,917; see the entire reference). This is a new rejection.

Essigmann et al teach a composition comprising a heterobifunctional genotoxic compound, which comprises a transcription factor decoy that mimics the endogenous genomic binding site of a sequence specific transcription factor, said transcription factor decoy being covalently bound to a genotoxic agent through a linker (e.g., column 8, line 25 to column 14, line 61; column 23, line 12 to column 24, line 13). Further, Essigmann et al teach the inclusion of a crosslinking agent (anchor moiety) attached to the decoy molecule (e.g., column 21, lines 8-20). Essigmann et al teach the use of linkers that contain up to about 20 or 30 carbon atoms (e.g., column 23, lines 26-67). Essigmann et al teach the use of poly(ethyleneglycol) (PEG) as a linker (e.g., column 23, lines 36-40). A PEG linker of 20 or 30 carbons would be at least 30 Å long. Essigmann et al teach providing the abovementioned heterobifunctional genotoxic compound. Essigmann et al teach the use of the linker to space apart the binding moieties for the transcription factor decoy and genotoxic agent such that the heterobifunctional compound can

sterically accommodate concurrent binding to the transcription factor and the cellular DNA (e.g., column 23, lines 40-44).

The claimed method recites that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target. However, the specification does not provide a specific description of characteristics of an entropically destabilized linker would possess except for length (e.g., page 39, line 16 to page 40, line 6). Since Essigmann et al teach linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional behavior on the nucleic acid target. As written the claim does not include a step that measures conditional behavior at different temperatures. With respect to the term "aptamer," the specification recognizes that the term "aptamer" generally refers to a double-stranded DNA or single-stranded RNA moiety that binds to a specific molecular target (see page 12, lines 13-15). However, the present specification defines the term "aptamer" to have a broader meaning encompassing a linker moiety that is dimensioned and configured to bind specifically with a small-molecule binding partner (see page 12, lines 15-18). The specification does not provide an explicit definition for the term, but indicates that it is broader than the definition usually given to the term. Accordingly, the term "aptamer" is reasonably interpreted to encompass other linker structures that do not necessarily bind a small-molecule.

Essigmann et al do not specifically teach the molecule where one an only one anchor moiety is included between the binding site for the transcription factor and the linker.

It would have been obvious to one ordinary skill in the art to include an anchor moiety, which is a crosslinking agent, between the transcription factor binding site and the linker moiety, because Essigmann et al teach compositions comprising each of these components and teach that the compound should be designed to sterically accommodate concurrent binding to the transcription factor and the cellular DNA.

One would have been motivated to use one anchor moiety between the target sequence for the transcription factor and the linker to provide distance between the binding site and the linker so as to sterically accommodate transcription factor binding to the target sequence in the presence of the linker moiety. Based upon the teachings of the cited reference, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 35, 36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al (US Patent No. 5,879,917; see the entire reference) as applied to claims 31, 32 and 34 above, and further in view of Ahern (The Scientist, Vol. 9, No. 15, page 20, July 1995, printed as pages 1/7-7/7; see the entire reference). This is a new rejection.

The teachings of Essigmann et al are described above and applied as before. Furthermore, Essigmann et al teach the use of numerous different genotoxic compounds that can be attached to the linker moiety of the compound (e.g., column 9, line 8 to column 11, line 43).

Essigmann et al do not teach providing a kit comprising instructions, and the compound where the genotoxic compound is not covalently attached to the linker, the compound being disposed in a suitable container.

Ahern teaches that products in kit form saves scientific investigators time and money (e.g., page 4/7, paragraph 2; page 5/7, paragraph 3). Ahern teaches that a kit can supply all of the necessary reagents for a particular research application and even provides detailed instructions (e.g., page 5/7, paragraph 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Essigmann et al to include the decoy-anchor-linker compound in a container in kit form with instructions because Essigmann et al teach it is within the ordinary skill in the art to use numerous different genotoxic agents which can separately be selected from the disclosed agents for attachment to the linker and Ahern teaches the provision of reagents in kit form with instructions.

One would have been motivated to make such a modification in order to receive the expected benefit of saving an investigator time and money as taught by Ahern, by eliminating the need to synthesize the decoy-anchor-linker compound. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-4, 6-10, 13 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al (US Patent No. 5,879,917; see the entire reference) as applied to claims 31, 32 and 34 above, and further in view of Hunt et al (US Patent No. 5,859,226; see the entire reference). This is a new rejection.

The teachings of Essigmann et al are described above and applied as before. Further, Essigmann et al teach that favorable properties of the decoy may be obtained by the use of nucleotide analogs or derivatives. Moreover, Essigmann et al teach the use of the linker to space apart the binding moieties for the transcription factor decoy and genotoxic agent such that the heterobifunctional compound can sterically accommodate concurrent binding to the transcription factor and the cellular DNA and suggests the use of electrophoretic mobility shift assays to detect binding (e.g., column 23, lines 40-44; column 34, lines 58-65).

Essigmann et al do not teach the use of nucleotide analogs that are polyamides. Essigmann et al do not specifically teach the use of the electrophoretic mobility shift assay to evaluate whether the linked genotoxic compound alters binding of the transcription factor to its binding site in the decoy molecule.

Hunt et al teach decoy molecules that contain a substitution of conventional bases with analogous forms of sugars, pureness and pyrimdines (e.g., column 13, lines 33-47). Hunt et al teach that alternative backbone structures such as polyamide backbone are particularly advantageous (e.g., column 13, lines 43-47). Hunt et al teach that two types of gel shift assays can be used to study binding of a transcription factor to a decoy molecule: the direct binding assay and the competition assay (e.g., paragraph bridging columns 23-24). The direct binding assay tests whether or not a radiolabeled polynucleotide decoy is able to directly bind a transcription factor, and the competition assay tests whether a decoy is able to compete with a radiolabeled control sequence for transcription factor binding (e.g., paragraph bridging columns 23-24).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the heterobifunctional compound of Essigmann et al to include the polyamide backbone, taught by Hunt et al, at least between the binding site and the linker because Essigmann et al teaches the use of nucleotide analogs in a decoy, and Hunt et al teach it is within the ordinary skill in the art to use a polyamide backbone in a decoy. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to assay the heterobifunctional compound of Essigmann et al for binding to a sequence-specific transcription factor, whose binding site is present in the decoy, because Essigmann et al teach that the compound should be designed to sterically accommodate transcription factor binding and Hunt et al teach that gel shift assays test for transcription factor binding

One would have been motivated to make such a modification in order to receive the expected benefit of providing a compound with the advantageous properties of the polyamide as taught by Hunt et al. Furthermore, one would have been motivated to test the compound for binding to the transcription factor in a gel shift assay to test for any steric hindrance caused by the genotoxic moiety in order to evaluate whether the linked genotoxic compound alters binding of the transcription factor to its binding site in the decoy molecule. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-3 and 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ansari et al (2001, of record) in view of Aurora et al (2002, of record). This rejection was made in the Office action mailed 11/29/2007 and is reiterated below.

Ansari et al teach an artificial transcriptional activator with a polyamide, non-protein DNA binding motif composed of heterocyclic residues that bind to the minor groove of DNA (see page 584, left column, 2nd paragraph, for example), which meets the limitation of an anchor moiety. Ansari et al teach that the polyamide, non-protein DNA binding motif is attached to a flexible polyether linker (i.e. oxygen atoms connected to two alkyl groups) (see page 584, left column, 3rd paragraph, and page 585, Fig 2, for example). Ansari et al teach linkers that are 12 and 36 atoms long (see page 585, Figure 2 legend). Ansari et al teach that the linker attaches the polyamide, non-protein DNA binding motif to an activating region (AH) of approximately 20 residues to form a conjugate (PA-1L-AH) (see page 584, left column, 3rd paragraph, for example), which meets the limitation of a linker moiety covalently bonded to the anchor moiety.

Ansari et al teach that the PA-1L-AH conjugate motif functions in a cell free system, and Ansari et al modified this conjugate motif to try to upregulate transcription. Ansari et al teach that the identity of the activating region was varied by size, identity and point of attachment to the polyamide. Ansari et al teach that the three activating regions tested were identified as AH, VP1 and VP2 (see page 584, Table 1 and page 587, left column, for example), which meets the limitation of a test compound, bonded to a linker moiety covalently bonded to a polyamide anchor moiety.

Ansari et al teach a plasmid vector with three cognate palindromic sequences upstream of an AdML TATA box, which is upstream of a G-less cassette (see page 591, left column, 2nd

paragraph). Using the broadest reasonable interpretation of a sequence specific regulatory factor-binding site, the TATA box meets the limitation of a known binding site for a sequence specific regulatory factor, since TATA box binding protein is known to bind the TATA box. Ansari et al teach that all of the varied conjugates bound to the cognate sites upstream from the AdML promoter (see page 586, left column), which meets the limitation of binding at a point proximate to, but not within the binding site (TATA box).

Ansari et al teach that the activating region is thought to bind to components of the transcriptional machinery that associate with RNA polymerase known as the RNA polymerase II holoenzyme (see page 583, right column). Ansari et al teach that a yeast nuclear extract was used as a reagent for the *in vitro* transcription assays (see page 591 left column section 4.3, in particular), which would comprise a natural transcription factor. Ansari et al teach that substituting the AH activator with VP2 increases the transcriptional activation strength of the conjugate over substitution with VP1 (see page 588, paragraph 2.4, for example), which meets the limitation of a step of contacting *in vitro* the nucleic acid target to a reagent mixture comprising one or more sequence-specific regulatory factors specific for the binding site defined in the nucleic acid target; and then determining whether binding of the sequence-specific regulatory factor to the binding site defined in the nucleic acid target is modulated by presence of the test compound.

Ansari et al does not specifically teach that the linker moiety is at least 30 Å long and entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target.

Arora et al teach artificial transcriptional activators comprised of a hairpin polyamide DNA binding domain and a peptide activation domain connected by flexible linkers of various lengths. Arora et al teach that the activation peptides used were AH and VP2, which have previously shown activation functionality when linked to a hairpin polyamide. Arora et al teach assays to determine the optimal length of the linker region in order to project the activating region away from the DNA in order to increase transcriptional activation. Arora et al teach that the linker plays a role in determining the ability of the activating region to stimulate *in vitro* transcription and that the optimal spacing between the DNA and the activating region is 36-45 Å (see page 13068, right column, in particular), which meets the limitation of a linker moiety that is at least 30 Å in length. Arora et al teach that this knowledge is important in order to be able to design functioning transcription factors.

The claimed method recites that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target. However, the specification does not provide a specific description of characteristics of an entropically destabilized linker would possess except for length (see 0161-0162, for example). Since Arora et al teach linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional behavior on the nucleic acid target. As written the claim does not include a step that measures conditional behavior at different temperatures.

It would have been obvious to the skilled artisan at the time of the invention to modify the compound taught by Ansari et al and to use a linker that is at least 30 Å in length because Ansari et al teach substitution of a native protein dimerization domain with a various length

flexible polylinker in order to modulate the function of a synthetic transcriptional activator (see page 584, left column, 3rd paragraph and page 587, left column, 2nd paragraph, for example) and Arora et al teach that 36-45 Å is an optimal linking region length. The motivation to use a 36-45 Å (at least 30 Å) linking region is the expected benefit of optimized transcriptional activation over the transcriptional activation observed using constructs comprising linking region of shorter or longer length. There is a reasonable expectation of success in using a linking region that is at least 30 Å long to increase transcriptional activation since it has worked previously in the cited reference. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore, Ansari et al (2001) in view of Arora et al render obvious a method of evaluating one or more test compounds to identify test compounds that modulate binding of sequence-specific regulatory factors to corresponding single-, double-, or triple-stranded nucleic acid binding sites, as recited in **claim 1**.

Ansari et al teach that the polyamide, non-protein DNA binding motif is attached to a flexible polyether linker (see page 584, left column, 3rd paragraph, and page 585, Fig 2, for example), which meets the limitation of the anchor moiety comprising a polyamide (**claim 2**).

Ansari et al teach that the DNA binding motif is attached to a flexible polyether linker (i.e. oxygen atoms connected to two alkyl groups) (see page 584, left column, 3rd paragraph, and page 585, Fig 2, for example), meets the limitation of a method wherein the linker moiety is selected from the group consisting of polypeptides, poly(ethyleneglycols), and C_{1-6} alkylenyl,

alkenyl, and alkynyl (**claim 7**) and selected from the group consisting of polypeptides, poly(ethyleneglycols), and C_{1-6} alkyl, alkene, and alkyne (**claim 8**).

Ansari et al teach attachment of a triplex forming oligonucleotide to a transcriptional activating region upregulated gene expression (see page 584, left column, 2nd paragraph, for example), which meets the limitation of the anchor moiety as a major groove-binding/triple helix forming oligonucleotide (**claims 3, 6 and 9**).

As previously discussed, the instant specification broadly defines aptamer as a linker moiety that is dimensioned and configured to bind specifically with a small-molecule binding partner. Ansari et al teach experiments in which the polyether linker had been conjugated at the C-terminus of the polyamide region, but that conjugation at an internal pyrrole residue is also effective (see page 587, left column, 2nd paragraph and page 589, right column, for example), which meets the limitation of a linker moiety that has been configured to associate with a binding partner. Therefore the linker rendered obvious by Ansari et al in view of Arora et al also meets the limitation of a method and a composition of matter wherein a linker moiety is an aptamer (**claim 10**).

Response to Arguments - 35 USC § 103

The rejection of claims 4, 13, 15-19, 31-32 and 34 under 35 U.S.C. 103(a) as being unpatentable over Ansari et al in view of Aurora et al has been withdrawn. The references do not teach the method where the isolated nucleic acid target is covalently bonded to an anchor moiety. The references teach anchor moieties that are non-peptidic DNA binding domains, which become conjugated to a nucleic acid target through non-covalent interactions.

The rejection of claims 5 and 14 under 34 under 35 U.S.C. 103(a) as being unpatentable over Ansari et al in view of Aurora et al is moot in view of Applicant's cancellation of the claims in the reply filed 5/22/2008.

With respect to the rejection of claims 1-3 and 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ansari et al (2001, of record) in view of Aurora et al (2002, of record), Applicant's arguments filed 5/22/2008 have been fully considered but they are not persuasive.

The response asserts that the rejection has been overcome by amendment of independent claim 1. The claim has been amended to recite that the target nucleic acid comprises "one and only one" known binding site or putative binding site, and "one and only one anchor." Further, claim 1 has been amended to exclude measuring recruitment of non-sequence specific transcriptional machinery. The response notes that the specification indicates that the present invention is not directed to measuring transcription *per se* but rather is directed to a method to examine the binding of a given regulatory factor to its cognate nucleic acid binding site and to insert into the reaction, at a location proximate to where the regulatory factor binds, a test compound that is physically linked to the nucleic acid target. The response points to Exhibit A as provide evidence that gene-specific transcription factors binding to defined DNA sequences near the start of transcription start controlled gene expression, and then a range of positive or negative regulatory signals are passed through numerous protein-protein contacts to RNA polymerase II. The response asserts that the claims exclude interactions with the transcriptional machinery because these interactions do not involve sequence-specific binding of a regulatory factor to its cognate site.

These arguments are not found persuasive. The claims do not positively set forth the action steps used to determine binding of a sequence-specific regulatory factor to the binding site defined in the nucleic acid target. The claims have been amended to exclude "measuring recruitment of non-sequence-specific transcriptional machinery." The response does not provide specific evidence that the reaction mix of Ansari et al does not contain a sequence-specific regulatory factor that binds the TATA box of the nucleic acid target. It was well known in the art at the time the invention was made that the TATA box sequence is recognized in a sequence-specific manner by the TATA-box binding protein (TBP), an essential factor involved in the initiation of transcription by all three eukaryotic DNA polymerases (Wang et al. PNAS, USA, Vol. 92, pages 8606-8610, September 1995; e.g., Abstract; page 8607, paragraph bridging columns; page 8609, left column, 1st full paragraph). The isolated nucleic acid target taught by Ansari et al comprises one and only one known binding site for TBP, a sequence-specific regulatory factor. Measuring transcription in the assay of Ansari et al is a measure of sequence-specific TBP binding and subsequent recruitment of the transcriptional machinery, and not just a measurement of non-sequence specific requirement of transcriptional machinery.

Ansari et al is not limited solely to evaluating interactions with non-sequence specific regulatory factors, and thus the rejection has not been overcome.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

The rejection of claims 22-28 under 35 U.S.C. 103(a) as being unpatentable over Ansari et al, as evidenced by Sadowski et al, in view of Aurora et al has been withdrawn. The references do not teach the method where the isolated nucleic acid target is covalently bonded to

an anchor moiety. The references teach anchor moieties that are non-peptidic DNA binding domains, which become conjugated to a nucleic acid target through non-covalent interactions.

The rejection of claims 13 and 15-18 under 35 U.S.C. 103(a) as being unpatentable over Ansari et al (2001) in view of Aurora et al and Ansari et al (2002) has been withdrawn. The references do not teach the method where the isolated nucleic acid target is covalently bonded to an anchor moiety. The references teach anchor moieties that are non-peptidic DNA binding domains, which become conjugated to a nucleic acid target through non-covalent interactions.

The rejection of claims 1, 3 and 6-9 under 35 U.S.C. 103(a) as being unpatentable over Ansari et al (2001) in view of Aurora et al and Ansari et al (2002) has been withdrawn. This rejection is moot in view of the rejection of claims 1, 3 and 6-9 under 35 U.S.C. 103(a) as being unpatentable over Ansari et al (2001) in view of Aurora et al.

The rejection of claims 22-28 under 35 U.S.C. 103(a) as being unpatentable over Ansari et al (2001), as evidenced by Sadowski et al, in view of Aurora et al and Ansari et al (2002) has been withdrawn. The references do not teach the method where the isolated nucleic acid target is covalently bonded to an anchor moiety. The references teach anchor moieties that are non-peptidic DNA binding domains, which become conjugated to a nucleic acid target through non-covalent interactions.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Celine X Qian Ph.D./

Primary Examiner, Art Unit 1636